

## Aging and Reproductive Potential in Women

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Reproductive potential in women declines with age. Age-related changes in the ovary account for most of this loss of reproductive function. Oocytes, all of which are present at birth, decline in number and quality with age. The endocrine function of the ovary also declines with age, and the ovary becomes unable to sustain its normal function in the neuroendocrine axis. The neuroendocrine axis may be further affected by primary changes occurring in the hypothalamus and pituitary during aging, although this has not been established in humans. Aging also affects the function of the uterus as the endometrium loses its ability to support implantation and growth of an embryo. Diminished uterine function during aging may be due to changes in the uterine vasculature or to changes in the hormone-dependent development of the endometrium. Finally, aging increases a woman's risk of developing medical, gynecologic or obstetric conditions that may impair her fertility. Knowledge of these affects of aging on a woman's reproductive function is essential to advise and treat the growing number of women seeking pregnancy at advanced reproductive age.

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### INTRODUCTION

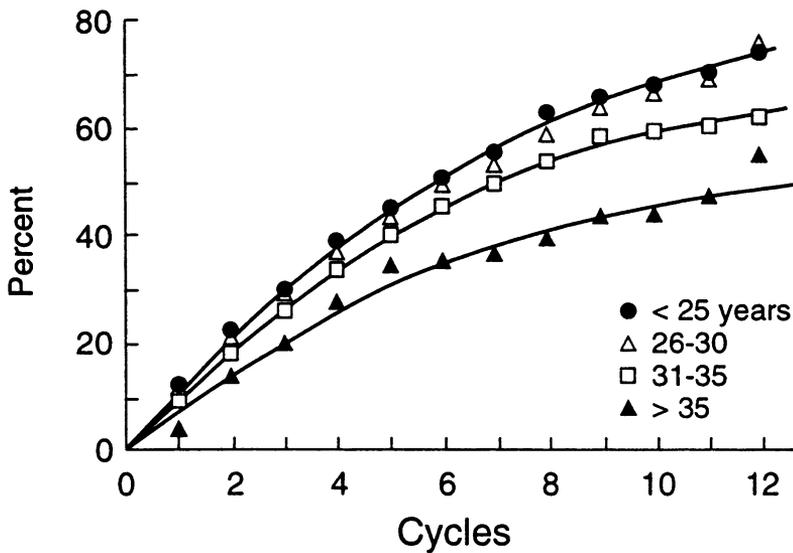
Despite the age-related decline in reproductive potential as women age, childbearing at advanced reproductive age has become increasingly common. In the United States in 1980, 19.8 births per 1000 were to women 35 to 39 years of age and 3.9 per 1000 were to those 40 to 44 years of age [1]. By 1996, these figures had risen to 35.4 and 6.8 per 1000, respectively. These are the highest birth rates observed for women in their 30s and 40s for more than two decades [2]. These increased birth rates in older women are attributed to a trend to delay childbearing due to improved educational and career opportunities as well as to the increased availability and use of contraception [1, 3].

Postponement of pregnancy allows women to achieve educational, career and financial goals before beginning a family. However, women who seek pregnancy at advanced reproductive age are more likely to experience difficulty achieving and maintaining a pregnancy, and delivering a healthy infant compared to their younger counterparts [4-7]. As early as 31 to 35 years of age, spontaneous cumulative pregnancy rates begin to decline. At 35 to 39 years of age, one-third of women experience difficulty achieving pregnancy and by 40 to 44 years of age, one-half of women have impaired ability to reproduce [8]. Spontaneous pregnancy rates approach zero soon after 45 years of age [9]. In donor insemination programs, cumulative success rates similarly decline with age (Figure 1) [10]. Less than 55 percent of women over the age of 40 achieve pregnancy within one year, compared to yearly pregnancy rates of 75 percent in women less than 30 years old

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<sup>b</sup>Abbreviations: IVF, *in vitro* fertilization; IVF-ET, *in vitro* fertilization and embryo transfer; GIFT, gamete intrafallopian transfer; ICSI, intracytoplasmic sperm injection; LH, luteinizing hormone; FSH, follicle stimulating hormone.



**Figure 1. Theoretical cumulative success rates of donor insemination in women of different ages with presumed normal fecundity.** (Mouzoun et al., 1988 [Ref. 10]. Reproduced with permission).

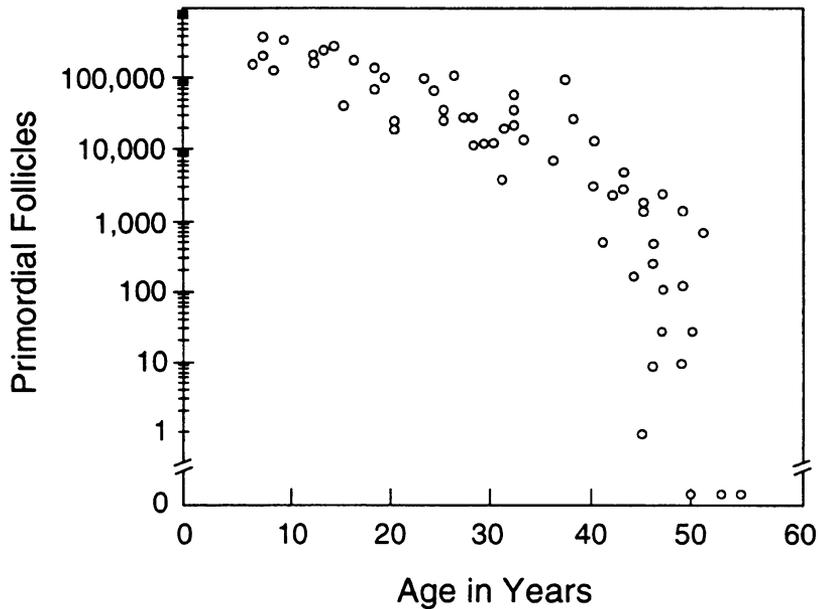
[11, 12]. In a large study specifically investigating the effect of age on pregnancy rates following *in vitro* fertilization and embryo transfer (IVF-ET)<sup>b</sup> and gamete intrafallopian transfer (GIFT), the pregnancy rate in women 25 to 39 years of age was 12.2 percent, and markedly declined to 7.3 percent in women 40 to 43 years of age, and to only 1.7 percent in those 44 to 45 years of age [13]. In IVF-ET, GIFT, and other assisted reproductive technologies, advanced age generally correlates with poorer therapy outcomes including a reduction in oocyte quality, fertilization rate, embryo quality, implantation rate per embryo and pregnancy rate [13-17] (Figure 1).

Today, at least 20 percent of women between 35 and 44 years of age seek fertility services. An understanding of what is currently known about the effects of age on reproductive potential is essential to appropriately advise, refer and treat women who seek pregnancy at advanced reproductive age. This article will review the major physiological changes occurring in the aging female reproductive system and will address how these changes affect female reproductive potential.

## AGE AND OOCYTES

### *Declining oocyte number*

Female gametes, or oocytes, are produced during embryogenesis after which they are gradually depleted during a woman's life. During early embryonic development, approximately 2,000 primordial germ cells migrate to the gonadal ridges. Rapid meiotic multiplication then occurs, and by 20 weeks of gestation, each ovary contains five to seven million follicles [18, 19]. Less than 0.1 percent (about 400) of the oocytes present at birth will actually be ovulated during a woman's reproductive life. The remaining oocytes will degenerate by atresia, a process that begins as early as 15 weeks of gestation and continues throughout a woman's life [20]. At approximately 37.5 years of age, when approximately 25,000 follicles remain, the rate of atresia doubles and results in an increased rate



**Figure 2. Relationship between age and primordial follicle number throughout life.** (Based on data reproduced from Block, 1952 [Ref. 18] and Richardson et al., 1987 [Ref. 21]).

of follicular loss during the perimenopausal period (Figure 2) [18, 21]. By the time of the menopause, which is at approximately 51 years of age, only about 1,000 follicles remain [22]. This observation has led some authors to conclude that a follicle count of 1,000 or less represents a threshold that triggers the cessation of menses. While this mechanism remains to be confirmed, the established relationship between the number of follicles remaining and reproductive function could be used to predict the time of a woman's menopause by counting the number of follicles in her ovaries using sonography. This approach, however, has not been applied clinically [23, 24]. The increasing rate of oocyte loss results in poorer success rates for women of advanced age undergoing IVF-ET because fewer oocytes are available for retrieval [25]. One study estimated that in women 24 to 32 years of age, the total number of oocytes retrieved declines by 1.25 oocytes per year [16] (Figure 2).

Although declining oocyte number certainly contributes to lower IVF-ET success rates in women of advanced reproductive age, a study that controlled for the number of oocytes retrieved per cycle demonstrated a persistent decline in pregnancy rates with age [16]. Thus, other factors, in addition to oocyte number, account for the reduced reproductive success of older women.

#### *Decreasing oocyte quality*

Oocyte quality deteriorates and results in impairment of reproductive function in women of advanced reproductive age [26]. For most of a woman's reproductive life, oocytes are arrested at a vulnerable stage of meiosis. Thus, oocytes are particularly sensitive to the deleterious effects of spontaneous mutations, endogenous hormones and toxic exposures [5, 27, 28].

The process of aging does not appear to affect the ability of older oocytes to fertilize, as many studies in the IVF-ET setting have demonstrated similar fertilization rates between older and younger women. Yet, lower implantation rates and higher spontaneous

**Table 1. Risk of spontaneous abortion related to maternal age.** (Warburton et al., 1986 [Ref. 29]. Reproduced with permission.)

Maternal age (Years)	Spontaneous abortion (Percent)
15-19	9.9
20-24	9.5
25-29	10.0
30-34	11.7
35-39	17.7
40-44	33.8
>44	53.2

abortion rates are observed among embryos derived from oocytes obtained from older women (Table 1) [29-31]. Oocyte age appears to specifically impair embryo implantation potential, which begins to decline gradually in women at 30 years of age and is reduced by half by 40 years of age [15] (Table 1).

The impaired ability of older oocytes to achieve the implantation and pregnancy success of younger oocytes is in part due to a predisposition of oocytes from older women to form aneuploid embryos. Aneuploidy, an example of which is trisomy, is a chromosomal abnormality that results from errors in chromosomal segregation during meiosis. The incidence of aneuploidy is highly correlated with maternal age. Compared to fetuses delivered by women 24 to 29 years of age, the incidence of aneuploidy increases by five percent in fetuses of women 30 to 35 years of age, and increases another five percent in those of women 36 to 39 years of age [32]. Only fifteen percent of all spontaneous abortions due to chromosomal trisomy occur in women under 25 years of age, compared to 33 percent among women 30 to 35 years of age, and to more than 65 percent for women over 40 years of age [32]. In IVF-ET, aneuploidy correlates with lower rates of oocyte fertilization and embryo implantation, poorer embryo development and decreased overall pregnancy potential [5, 33]. Aneuploidy is a result of either nondisjunction of bivalent chromosomes or pre-division of sister chromatids at meiosis I [34]. A recent study suggested that increased maternal age specifically predisposes oocytes to undergo pre-division of sister chromatids at the first meiotic maturation division [35]. This is supported by the observation that the meiotic spindle is frequently abnormal in oocytes of older women [36]. Cumulative luteinizing hormone (LH) exposure, which increases with age, may be one factor responsible for the age-related increase in aneuploidy [28]. In animal models, when oocytes are subjected to prolonged exposure to LH *in vitro* and *in vivo* by delaying fertilization, high aneuploidy rates and poor survival rates are seen in the resulting embryos [37, 38]. In humans, a similar process may occur as increasing the interval between ovulation and insemination results in a higher incidence of spontaneous abortion [39]. Alternatively, according to the "production line" hypothesis, fetal aneuploidy may be pre-determined during the time of oocyte formation, which occurs during late fetal life. According to this hypothesis, the last oocytes formed have fewer chiasmata and more univalent pairs (which are associated with trisomy) and coincidentally are the last oocytes to be ovulated during a woman's life [40].

Oocyte degeneration, which is the spontaneous splitting of chromosomes into two distinct chromatids, also appears to be related to age. Aging oocytes *in vitro*, though distinct from biological aging, results in increased rates of chromosome fragmentation [41]. Cytogenetic analysis of oocytes that fail to fertilize in patients undergoing IVF-ET and/or

intracytoplasmic sperm injection (ICSI) reveals a significant increase in chromosome degeneration in oocytes from older women compared to those obtained from younger women [31]. Additionally, gene fragmentation and gross abnormalities are more common in pre-embryos derived from oocytes of women older than 35 years of age [42].

## AGE AND THE REPRODUCTIVE NEUROENDOCRINE SYSTEM

The female reproductive neuroendocrine system is composed of the ovarian-hypothalamic-pituitary axis. End organ products secreted by the ovary, including estradiol, progesterone, and inhibin, function as feedback signals to the hypothalamus and pituitary. Numerous complex changes occur in the female reproductive system during aging. In natural reproductive cycles, the ovary requires FSH for normal follicular recruitment and folliculogenesis. During the luteal phase of the previous cycle, the function of the corpus luteum wanes and estradiol and progesterone levels decline [43]. Decreased estradiol and progesterone levels allow increased FSH secretion, which stimulates the ovary and results in the growth and development of a cohort of follicles for the next cycle [44]. As this cohort of follicles grows and estradiol begins to rise, FSH secretion is gradually suppressed as a result of estradiol positive feedback to the hypothalamic-pituitary system [44].

### *Rising gonadotrophin levels and aging*

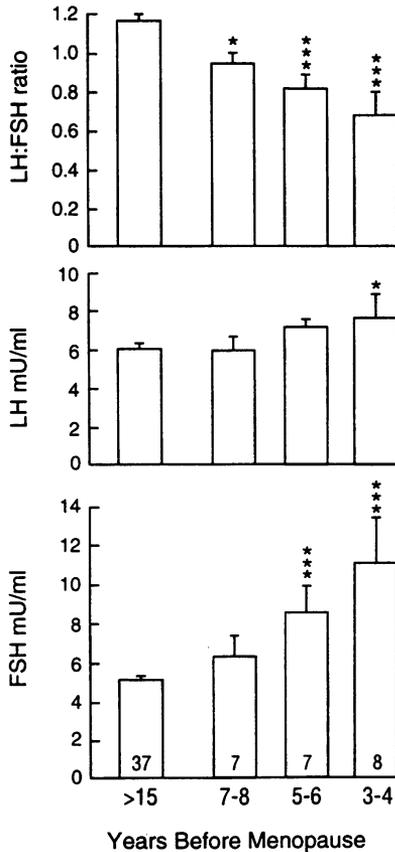
Small increases in follicle stimulating hormone (FSH) secretion are seen in women as early as their mid-30s at the time of onset of the perimenopausal period [45]. Basal LH concentrations also rise during the perimenopause, although increases in basal FSH levels occur up to five years before a rise in LH secretion can be detected (Figure 3) [46-48]. Increased levels of FSH and LH during aging are associated with decreased fertility [45, 49] (Figure 3).

The elevated levels of FSH and LH seen during the perimenopausal period are believed to reflect waning function of the ovary. The aging ovary loses its ability to respond to normal FSH levels and to produce appropriate levels of estrogen and progesterone to serve as down-regulatory signals to the hypothalamic-pituitary system. It has been suggested that high FSH levels may be in part responsible for the accelerated depletion of primordial follicles seen in the ovary during the perimenopause [21]. High LH levels may cause deleterious effects on the developing oocyte such as accelerated or early maturation [50]. Increased LH secretion may also cause supraphysiological androgen production by the theca cells and follicular atresia [51, 52].

During the perimenopausal period, ovulation continues to occur and cycles are potentially fertile but tend to become less regular. Such changes in the characteristics of a woman's menstrual cycle may become apparent five to 10 years before she has had her last menstrual period [21]. As a woman approaches menopause, the frequency of anovulatory cycles increases, until ultimately menstruation ceases. The mechanism of menopause is poorly understood, but numerous factors are believed to affect its onset. For example, good nutrition [53] and high parity [54] are associated with a later menopause, whereas smoking and African-American heritage are associated with earlier menopause [55]. It is interesting to note that despite these life-style, environmental and sociological effects, the age of menopause has not changed since the middle ages [56].

### *Gonadotrophin and sex steroid secretion during aging*

The relationship between the age-related changes in gonadotropin secretion and the secretion of sex steroids by the ovary is not clear. Increased secretion of LH and FSH occurs in cycles in which peri-ovulatory secretion of estradiol and luteal phase secretion



**Figure 3.** Geometric means ( $\pm$  error of the mean) of plasma LH and FSH concentrations and the LH/FSH ratio measured in 59 women and presented in relation to years before the menopause. (Lenton et al., 1988 [Ref. 48]. Reproduced with permission).

of progesterone are maintained [49]. Some studies have shown that estradiol levels increase during the perimenopausal period. Increased estradiol secretion during the perimenopausal period can be explained by increased follicular recruitment [57, 58]. In contrast, one large study measured daily serum levels of estradiol and progesterone in healthy women with normal menstrual cycles and observed no aged-based differences in estradiol and progesterone production at ages ranging from 24 to 50 years [49]. The monotropic rise in FSH secretion in the presence of normal LH levels is enigmatic since estradiol levels remain high and since FSH secretion is more sensitive to negative feedback by estradiol than is LH [59]. Although estradiol is a primary regulator of FSH secretion [60], other factors account for the changes in gonadotropin secretion that occur during the perimenopause.

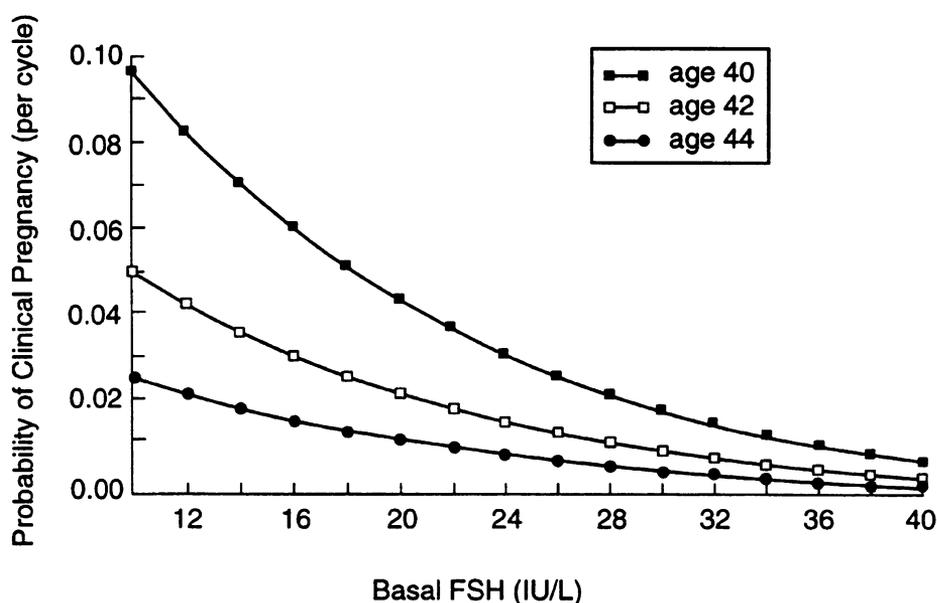
#### *Inhibin production and aging*

It is thought that elevated concentrations of FSH during the menopause may be a result of reduced secretion of inhibin [61]. Inhibin is a glycoprotein molecule secreted by granulosa cells of the follicle during the follicular phase of the menstrual cycle and by the granulosa-lutein cells of the corpus luteum during the luteal phase [62, 63]. Although inhibin selectively suppresses FSH secretion [64], it has been suggested that inhibin also acts as a trigger for FSH secretion at the end of the luteal phase [65] and is, therefore, obligatory for folliculogenesis. A decreased inhibin level may be used as a marker of waning ovarian function [66, 67]. Lower follicular phase inhibin levels have been demonstrated in older women [63] in association with increased FSH levels. Other data from assisted conception

cycles reveal that inhibin levels are significantly reduced in older women during cycles in which maximum estradiol levels are unchanged [68].

*Reproductive aging: in the ovary or the hypothalamic-pituitary axis?*

It is generally believed that declining function of the ovary accounts for most, if not all, of the age-related changes in the human reproductive system. The effects of age observed in the hypothalamus and the pituitary are believed to be secondary. In rodents, however, primary age-related effects in the hypothalamus and the pituitary have been demonstrated [69]. When aged rat ovaries are transplanted into younger females, the ovaries temporarily resume cyclic function under the influence of a younger hypothalamic-pituitary system [70]. Pituitary sensitivity to estradiol feedback is decreased in aging rats, probably due to a reduction in the number of estradiol receptors [71]. In addition, studies of the hypothalamus in older rats reveal decreased ability to appropriately release gonadotrophin releasing hormone [72-74]. However, the applicability of the rat as a neuroendocrine model for human female aging has been questioned since conflicting findings have been observed in humans. Compelling evidence that age has no direct effect on the reproductive function of the human hypothalamic-pituitary axis is provided by a study examining the effects of aging in oophorectomized women [72]. This study revealed that in the absence of ovaries, the concentration and pulse pattern of gonadotropin release do not differ among women between 27 and 64 years of age [72]. In contrast, a recent study demonstrated different patterns of release of hypothalamic and pituitary hormones in women with idiopathic premature ovarian failure compared to older post-menopausal women [73]. The central hypothalamic effects of aging may be explained by age-related slowing of the gonadotropin releasing hormone pulse generator [74].



**Figure 4. Clinical pregnancy rate per cycle as a function of both basal FSH and chronological age for women 40 and older undergoing ovulation induction. (Pearlstone et al., 1992. Reproduced with permission).**

### *Neuroendocrine function and reproductive success*

The relationships between age-related changes in the ovary, hypothalamus and the pituitary and the decline of reproductive potential remain to be defined. However, assessment of the neuroendocrine system as a whole is helpful in predicting reproductive success. Various methods have been developed to assess neuroendocrine function to estimate the likelihood of success for women of advanced age undergoing assisted conception. Currently, the most readily available and minimally invasive method is the determination of basal FSH levels on day 3 of a woman's menstrual cycle [75]. In women undergoing IVF, pregnancy rates decrease as FSH levels increase (Figure 4) [76]. Although interpretation of serum levels of FSH must be institution specific due to assay variation, favorable or non-favorable prognosis for women undergoing assisted conception may be estimated by using carefully selected cut-off levels [77]. Some authors have suggested that determination of basal FSH levels in conjunction with the age of the patient and number of previous treatment cycles can improve the predictive value of this test [78, 79]. In addition, increased LH levels, especially in association with increased FSH may predict poor pregnancy rates and high rates of spontaneous abortion [80, 81]. Elevated basal estradiol levels or decreased serum inhibin levels may also be used to predict impaired reproductive function when in the presence of elevated basal FSH levels [82] (Figure 4).

More invasive methods to assess reproductive neuroendocrine function in aging women have been developed as well. Elevated basal FSH levels in response to challenge with the anti-estrogen, clomiphene citrate, correlate with decreased pregnancy rates. Although the rate of abnormal tests increases with age, the utility of the clomiphene challenge test is limited in older women because the age-related decline in reproductive potential precedes the development of an abnormal test [75]. Another test involves the subcutaneous administration of a gonadotropin releasing hormone agonist. The estradiol response is then evaluated in conjunction with other parameters such as the age of the patient and the number of follicles present to estimate reproductive potential. This gonadotrophin-releasing hormone stimulation test has been implemented in only a single institution and its general applicability remains to be determined [75].

## **THE UTERUS AND AGING**

Just as many organs suffer the consequences of aging, evidence suggests that age-related changes occurring within the uterus may affect endometrial receptivity to embryo implantation and embryo growth and result in reduced fertility. Uterine receptivity is dependent upon priming of the endometrium by estradiol. This priming involves the production of endometrial proteins and glycoproteins such as estrogen and progesterin receptors during the follicular phase [83]. Although endometrial morphology appears to be unaffected by low luteal phase estrogen levels, increased estrogen levels do enhance uterine perfusion through increased vasodilation [84]. Changes in steroid secretion may increase uterine and endometrial blood flow and, thereby, increase endometrial receptivity, although no direct evidence for changes in uterine vascular resistance with age has been demonstrated [85, 86]. In rodents, age-related decline in fertility is attributed in part to uterine factors [90-92]. Diminished uterine function during aging is supported by findings of age-related decreases in the number of endometrial estrogen and progesterone receptors [90] and age-related increases in collagen deposition and fibrosis in the rat endometrium [91]. In humans, no consensus has been reached regarding the effect, if any, of age-related diminution in uterine receptivity on reproductive function.

### *Luteal phase deficiency and decreased uterine receptivity*

Luteal phase deficiency, by definition, is insufficient progesterone production by the corpus luteum, which results in inadequate maturation of the endometrium [92]. Progesterone is necessary for implantation and the maintenance of pregnancy [93, 94]. While some data show no difference in ovarian steroid production in women of different ages [95], other studies have revealed lower luteal-phase progesterone secretion in older women [73], which is supported by the reduced ability of granulosa-lutein cells from older women to produce progesterone *in vitro* [67].

Luteal phase deficiency appears to be associated with abnormal folliculogenesis. Some data have revealed a reduction in peak follicle diameter in older women with lower pregnancy rates, reduced luteal phase progesterone secretion and an increased incidence of luteal phase deficiency [99-102]. A shortened follicular phase is also associated with a deficient luteal phase in older women [103-105]. Thus, luteal phase deficiency may contribute to abnormal folliculogenesis with aging and result in higher rates of infertility and recurrent abortion. [103, 104].

Folliculogenesis may be abnormal in patients with luteal phase deficiency due to increased resistance to blood flow in the intra-ovarian vessels. Increased resistance in ovarian vessels could result in a relative reduction in blood flow to the corpus luteum [105]. In monkeys, however, inappropriate gonadotropin secretion causes abnormal folliculogenesis and luteal phase deficiency [106]. In humans, some investigators have found luteal phase deficiency associated with abnormal LH surges [96, 100]. Others have suggested that luteal phase deficiency is associated with alterations in LH pulse frequency during the follicular phase [107]. LH binding sites are present within the endometrium and it is thought that elevated LH levels, which are seen during the follicular phase and at advanced age, may have adverse effects on endometrial development [108].

### *The donor oocyte model*

Donor oocyte programs provide the optimal setting to study the role of age-related changes in the uterus on reproductive potential because the confounding variables of oocyte age and number are removed and the uterine contribution to reproductive potential may be assessed independently. A report of successful pregnancy and delivery in a 63-year-old recipient of donated oocytes clearly demonstrates that the uterus can support pregnancy far beyond the age at which ovarian competence normally ceases [109]. Studies from donor oocyte programs reveal similar implantation, pregnancy, miscarriage, and delivery rates among donor oocyte recipients of different ages and clearly demonstrate that the aging uterus and endometrium are fully capable of supporting embryo implantation and of maintaining pregnancy. [85, 113-115,]. However, a contribution of uterine factors to age-related infertility are not precluded by these findings because the donor oocyte recipients in these programs were treated with supra-physiological levels of progesterone, which may reverse or overcome the age-related changes in the endometrium. To adequately address this issue, recipients would need to be treated with normal physiological doses of progesterone [8, 110, 113, 114]. In one study, a higher pregnancy loss rate was observed in recipients over 40 years of age and correlated with retarded placental secretion of estradiol and progesterone [114].

## CONCLUSION

As more and more women delay childbearing until the latter part of their reproductive lives, understanding the effects of age on the female reproductive system has become increasingly important. It is clear that aging impairs a woman's capability to achieve and

maintain pregnancy, through both natural and assisted methods. Much of this loss in reproductive potential is accounted for by age-related changes within the ovary. These changes include a progressive decline in the number of oocytes available for ovulation or retrieval, as well as a progressive decline in the capacity of these oocytes to form viable healthy embryos. In addition, the endocrine function of the ovary is affected by age and the feedback mechanisms involving FSH, LH and inhibin become significantly altered. Increased serum FSH signals the onset of these changes and is used as a marker of declining reproductive potential. While most age-related changes in the human female reproductive neuro-endocrine system are thought to be secondary to the waning endocrine function of the ovary, some evidence suggests that primary changes occur with age in the hypothalamus and the pituitary as well. Finally, reproductive potential appears to be affected by age-related changes in the uterus. Changes in luteal phase hormonal support of the uterine lining, or changes in blood supply to the uterus may be responsible for the age-related decline in uterine receptivity. However, through the administration of supra-physiologic doses of progesterone in donor oocyte programs, these effects of age on the uterus can be overcome.

The normal physiological aging processes of the ovary, neuroendocrine axis and uterus result in a general decline in reproductive potential in healthy women as they age. In addition, age may further affect a woman's reproductive potential by increasing her susceptibility to pathologic conditions that adversely affect fertility, pregnancy, and fetal outcome. Fertility is impaired by diseases of the reproductive organs such as endometriosis, leiomyomas of the uterus, infectious tubal peritoneal disease, and cancers of the uterus or ovary, all of which increase in incidence with age [115, 116]. The incidences of gestational diabetes, preeclampsia, placenta previa, abnormal labor, Cesarean section and operative deliveries also increase with age [6]. Additionally, gravidas over the age of 35 are at a much higher risk for fetal morbidity and mortality than those younger than 30 years of age [7, 117].

Applying what is known about the physiological effects of aging on the female reproductive system will be helpful in the advisement and treatment of women seeking pregnancy at an advanced maternal age. However, the specific mechanisms underlying many of the age-related changes in the ovary, neuroendocrine axis and uterus have not been established. Further research is necessary to better understand the normal reproductive physiology of women of advanced reproductive age and to better care for this growing population.

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